REMARKS

Information Disclosure Statement

The Examiner stated that all of the references submitted in an Information Disclosure Statement on October 14, 2009 were considered except for the Genbank and Press Release citations. The Examiner stated that legible copies of these references were not submitted. Applicants however note that the Genbank and Press Release documents appear on the Patent Application Information Retrieval portal and are legible. The Genbank citations correspond to the 11th - 13th NPL documents with a "Mail Room Date" of October 14, 2009. The Press Release citations correspond to the 14th - 40th and 54th NPL documents with a "Mail Room Date" of October 14, 2009. As legible copies of these citations were provided with the October 14, 2009 Information Disclosure Statement, Applicants respectfully request consideration of these citations.

Amended Claims and Support

Claims 1-20, 22 -34 and 52-55 are currently pending in this application. Claims 1-17 and 52-55 have been withdrawn from further prosecution by the Examiner as being directed to a non-elected invention. Claims 19, 20, 22, 27-31 and 34 are hereby cancelled without prejudice or disclaimer. Pending claims 18 and 32 have been amended as indicated below. New dependent claims 56 to 71 have been added to claim additional embodiments of the invention. Support for the amendments and new claims can be found throughout the application as filed, as described in more detail below. No new matter has been added by way of the claim amendments and new claims.

Claim 18, currently on file, has been amended to incorporate elements of dependent claims 22, 31 and 34, to specify that the one or more cytokines are selected from interferon alpha and interleukin-2, and to recite that "a combination of said antisense oligonucleotide and said one or more cytokines is more effective in treating cancer than either component of the combination when used alone." Support for these

amendments can be found throughout the specification as filed, for example at page 1, lines 2 to 13; at page 28, lines 29 to 30; at page 29, line 20; at page 41, lines 20 to 25, and in Examples 2 to 7 and 10.

Claim 32, currently on file, has been amended for consistency in view of the amendments to independent claim 18.

New claims 56 to 59 recite specific lengths for the antisense oligonucleotide as set forth in claim 18. Support for these new dependent claims can be found throughout the specification as filed, for example at page 17, lines 9 to 14.

New claims 60 to 61 specify that the antisense oligonucleotide comprises or consists of SEQ ID NO:1. Support for these new dependent claims can be found throughout the specification as filed, for example, at pages 13 to 17.

New claims 62 to 63 are directed to modes of administration of the antisense oligonucleotide. Support for these new dependent claims can be found throughout the specification as filed, for example, at page 46, lines 21 to 22.

New claims 64 to 65 are directed to specific types of cytokines. Support for these new dependent claims can be found throughout the specification as filed, for example, at pages 59 to 77 (Examples 1 to 11).

New claims 66 to 67 are directed to modes of administration of the cytokines. Support for these new dependent claims can be found throughout the specification as filed, for example, at page 64, lines 22 to 23.

New claims 68 to 70 are directed to specific types of cancers. Support for these new dependent claims can be found throughout the specification as filed, for example, at page 45, lines 4, 14, 16 and 26; page 46, line 4, and pages 59 to 77 (Examples 1 to 11).

New claim 71 specifies that the combination of the antisense oligonucleotide and the one or more cytokines produces an at least additive effect on one or more of tumour shrinkage, time to progression or survival. Support for this new dependent claim can be found throughout the specification as filed, for example, at page 1, lines 2 to 13; at page 43, lines 20 to 25, and in Examples 2 to 7 and 10.

Priority

The Examiner has maintained the rejection of the benefit of U.S. Application Serial No. 60/535,496 filing date for claims 18-20, 22-30 and 32-34 as failing to provide adequate written description for the claimed subject matter under the first paragraph of 35 U.S.C. §112 and has reiterated that the benefit of an earlier filing date for claims 18-20, 22-30 and 32-34 is granted only insofar as the filing date of U.S. Application Serial No. 60/602,817, which is August 18, 2004. The Examiner stated that at best, the disclosure of U.S. Application Serial No. 60/535,496 provides written description for the method step of administering one or more cytokines; but alleged that it fails to provide adequate support for the claimed method encompassing the entire genus of immunotherapeutic agents as well as the specifically enumerated species in the manner provided by the first paragraph of 35 U.S.C. §112.

Applicants respectfully disagree with the Examiner's position for the reasons set forth in Applicants' previous correspondence filed September 22, 2009. Solely in order to expedite prosecution of the subject application, however, pending independent claim 18 has been amended to recite:

"A method of treating cancer in a human comprising administering to said human:

(a) an antisense oligonucleotide of between 7 and 50 nucleotides in length comprising at least 7 consecutive nucleotides of the sequence as set forth in SEQ ID NO.:1, and

(b) one or more cytokines selected from interferon alpha and interleukin-2,

wherein a combination of said antisense oligonucleotide and said one or more cytokines is more effective in treating cancer than either component of the combination when used alone."

Claims 19, 20, 22, 27-31 and 34 have been cancelled without prejudice or disclaimer, thereby rendering moot the Examiner's rejection as it applies to these claims.

As noted by the Examiner, U.S. Application Serial No. 60/535,496 provides written description for a method step of administering one or more cytokines. Applicants note that U.S. Application Serial No. 60/535,496 also clearly describes the use of interferons and interleukin-2 in combination with the recited antisense oligonucleotide (see, for example, page 15, lines 9 to 11, and page 16, lines 3 to 8, of U.S. Application Serial No. 60/535,496). Applicants assert, therefore, that amended independent claim 18 and claims dependent thereon are entitled to the benefit of the filing date of U.S. Application Serial No. 60/535,496, i.e., January 12, 2004.

Claim Rejections under 35 U.S.C. § 102 – Anticipation

The Examiner has maintained the rejection of claims 18-20, 23, 25, 28-29 and 33-34, under 35 U.S.C. § 102(b) as being anticipated by Wright *et al.*, in WO 98/00532 (hereinafter referred to as "Wright-A"). The Examiner had previously argued that Wright-A teaches a method of treating a metastatic cancer or a solid cancer in a mammal comprising administering a pharmaceutical composition comprising 1) a phosphorothioate-modified antisense oligonucleotide that is at least 7 consecutive nucleotides complementary to SEQ ID NO:43, which is 39 nucleotides in length and is complementary to nucleotides 2007-2045 of SEQ ID NO:105 of the instant application and 2) specific antibodies such as monoclonal antibodies, wherein the mammal is a human (referring to pages 7, 11, 13-16 and claims 7, 8, 10-13, 26-30). The Examiner stated that Applicants' arguments filed on September 22, 2009, have been fully considered but are not persuasive.

Applicants respectfully disagree with the Examiner's position for the reasons set forth in Applicants' previous correspondence filed September 22, 2009. Solely in order to expedite prosecution of the subject application, however, Applicants have amended independent claim 18 as noted above to specify that the method of treating cancer comprises administering "an antisense oligonucleotide of between 7 and 50 nucleotides

in length comprising at least 7 consecutive nucleotides of the sequence as set forth in SEQ ID NO.:1" and "one or more cytokines selected from interferon alpha and interleukin-2." Claims 19, 20, 22, 27-31 and 34 have been cancelled without prejudice or disclaimer, thus rendering moot the Examiner's rejection as it applies to these claims.

Wright-A fails to disclose a method of treating cancer using an antisense oligonucleotide and one or more of the cytokines recited in amended independent claim 18. Therefore, amended independent claim 18 and claims dependent thereon, are not anticipated by Wright-A and respectfully request that this rejection be withdrawn.

Claim Rejection - 35 USC §103 – Obviousness

The Examiner has maintained the rejection of claims 18-20 and 22-34 under 35 U.S.C. § 103(a) as being unpatentable over Wright *et al.* (US 5,998,383) (hereinafter referred to as "Wright-B") in view of Pavlick *et al.* (*Expert Opinion on Investigation Drugs,* 2003, 12:1546-1558) (hereinafter referred to as "Pavlick").

The Examiner stated that Applicants' arguments filed on September 22, 2009 have been fully considered but are not persuasive. In particular, the Examiner stated that there is no requirement in the claims as currently written that the combination of antisense oligonucleotide and a cytokine must result in a "better" treatment effect compared to single agent therapy. The Examiner further stated that combination therapeutic strategies for treating cancer (e.g., combination of an antisense oligonucleotide and a chemotherapeutic agent; combination of chemotherapy and immunotherapy) were known in the art as taught by Wright-B and Pavlick.

With respect to Applicants' position that Pavlick alone or in combination with Wright-B does not teach combination of an antisense oligonucleotide with a cytokine, the Examiner stated that an antisense oligonucleotide (G3139 of Genasense listed in Table 2 of Pavlick) was a known anti-cancer therapeutic agent that can be effectively used in combination with chemotherapeutic agents as G3139 in combination with decarbazine, was under the phase III clinical trial at the time the invention was made, and that the

instantly claimed antisense oligonucleotide targeted against SEQ ID NO:1 was an art-recognized anti-cancer agent that can be used in combination with a chemotherapeutic agent as taught by Wright-B. The Examiner alleged therefore that since the anti-cancer therapeutic efficacy of chemotherapeutic agents was known to be improved when combined with a cytokine as taught by Pavlick, it would have been obvious to one of ordinary skill in the art to further add a cytokine to the dual combination therapy comprising an antisense oligonucleotide and a chemotherapeutic agent. The Examiner noted that claim 32 specifically requires all three agents, and claim 18 does not exclude a chemotherapeutic agent as the method recites the open-ended transitional phrase "comprising".

The Examiner further alleged that the improved therapeutic effects for cancer treatment via a combination therapy compared to monotherapy were sufficiently suggested in the art as taught by Pavlick (referencing page 1553) and as such, that Applicants' asserted improved cancer growth inhibition is not unexpected. The Examiner also alleged that the passages pointed out by Applicants do not show the asserted unexpected results that are commensurate in scope with the claims as they show a combination of the antisense oligonucleotide with a very specific species of immunotherapeutic agents (IL-2 or IFN alpha) and with a very specific species of chemotherapeutic agent (mitomycin C or CPT-11 or 5-FU).

Applicants respectfully disagree with the Examiner's position for the reasons set forth in Applicants' previous correspondence filed September 22, 2009. Solely in order to expedite prosecution of the subject application, however, Applicants have amended independent claim 18 as noted above to specify that the method of treating cancer comprises administering "an antisense oligonucleotide of between 7 and 50 nucleotides in length comprising at least 7 consecutive nucleotides of the sequence as set forth in SEQ ID NO.:1" and "one or more cytokines selected from interferon alpha and interleukin-2." Claim 18 has been further amended to recite that "a combination of said antisense oligonucleotide and said one or more cytokines is more effective in treating

cancer than either component of the combination when used alone." Claims 19, 20, 22, 27-31 and 34 have been cancelled without prejudice or disclaimer, thus rendering moot the Examiner's rejection as it applies to these claims.

Insofar as Examiner's rejection is maintained against amended independent claim 18 and claims dependent thereon, Applicants respectfully traverse for the following reasons. Pavlick describes the use of a combination of a chemotherapeutic agent with a cytokine in the treatment of cancer. Pavlick does not teach a combination of an antisense oligonucleotide and one or more cytokines as required by amended claim 18, nor does Pavlick teach or suggest that a combination of the antisense oligonucleotide and the one or more cytokines would be more effective in treating cancer than either component of the combination when used alone.

Wright-B describes the use of an antisense oligonucleotide optionally in combination with chemotherapeutic drugs in the treatment of cancer. Wright-B also fails to teach or suggest a combination of an antisense oligonucleotide and one or more cytokines that is more effective in treating cancer than either component of the combination when used alone, as required by amended claim 18. Even if the skilled worker were to consider combining the cytokine taught by Pavlick with the combination of antisense oligonucleotide and a chemotherapeutic taught by Wright-B, as alleged by the Examiner, this would, as also noted by the Examiner, result in a combination of three agents. Applicants assert that there is nothing in either of these two references that suggests that a combination of an antisense oligonucleotide and a cytokine would demonstrate an improved efficacy.

For the reasons outlined above, Applicants assert that Wright-B in combination with Pavlick fails to teach or suggest a method of treating cancer with a combination of an antisense oligonucleotide targeted to ribonucleotide reductase R2 with interferon alpha and/or interleukin-2, as recited in amended independent claim 18. Applicants further assert that the skilled worker, in view of these references, would not have a reasonable expectation that a combination of this antisense oligonucleotide and the one or more

cytokines would be more effective in treating cancer than either component of the combination when used alone. Accordingly, Applicants assert that the combination of Wright-B, in view of Pavlick, fails to render the subject matter of amended independent claim 18 and claims dependent thereon obvious and that these claims, therefore, comply with 35 USC §103(a).

Claim Rejection - 35 U.S.C. § 103 – Obviousness

The Examiner rejected claims 18-20 and 22-34 under 35 U.S.C §103(a) as being unpatentable over Seheult *et al.* (*Abstracts of the General Meeting of the American Society for Microbiology,* 2002) (hereinafter referred to as "Seheult"), Auer *et al.* (*43rd Annual Meeting of the American Society of Hematology*, 2001) (hereinafter referred to as "Auer"), Abaza *et al.* (*Annual Meeting of the Federation of American Societies for Experimental Biology*, 2001) (hereinafter referred to as "Abaza"), in view of Wright *et al.* (WO 00/47733) (hereinafter referred to as "Wright-C").

The Examiner stated that Seheult teaches that an antisense oligonucleotide targeted to TGF-beta1 in combination with IL-12 synergistically enhances the anti-tumour effect of the antisense oligonucleotide; Auer teaches that an antisense oligonucleotide targeted to Bcl-2 (G3139 of Genasense) in combination with rituximab or dexamethoasone or fludarabine confers enhanced anti-tumour activity and that the antisense oligonucleotide is synergistic with the immunotherapeutic agent, and Abaza teaches that one can improve cancer treatment effects by combining an antisense oligonucleotide targeted to C-myb with either a standard cytotoxic (chemotherapeutic) agent or immunotherapeutic agent such as IFN gamma and IFN beta.

The Examiner acknowledged that none of Seheult, Auer or Abaza teaches using an antisense oligonucleotide targeted to ribonucleotide reductase R2. The Examiner stated that Wright-C teaches that an antisense compound "AS-II-626-20" that has the nucleotide sequence of "GGCTAAATCGCTCCACCAAG", which is identical to the claimed sequence of SEQ ID NO.:1, effectively inhibits tumor cell proliferation *in vivo* in mice

and that the "AS-II-626-20" compound is more effective in reducing tumor volume/weight than antisense compounds targeted to Bcl-2 or C-myb. The Examiner alleged that it would therefore have been obvious to one of ordinary skill in the art at the time the invention was made to administer the "AS-II-626-20" compound in combination with any art-recognized anti-cancer, immunotherapeutic agent, further in combination with a chemotherapeutic agent. The Examiner alleged that one of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success because combination therapeutics comprising different classes of anti-cancer agents, especially antisense oligonucleotides in combination with immunotherapeutic agents or chemotherapeutic agents were known to confer synergistic cancer treatment effects as taught by Seheult, Auer, and Abaza. The Examiner further alleged that since the "AS-II-626-20" compound was known to be more effective in reducing tumor weight/volume in mice than the anti-Bcl-2 antisense oligonucleotide of Auer, or the anti-C-myb antisense oligonucleotide of Abaza, one of ordinary skill in the art would have been motivated to replace the anti-Bcl-2 or anti-C-myb antisense oligonucleotide with "AS-II-626-20" compound of Wright-C in the combination cancer therapy methods of Auer and Abaza.

Without conceding to the correctness of the Examiner's position, but solely in order to expedite prosecution of the subject application, Applicants have amended independent claim 18 as noted above to specify that the immunotherapeutic agents are "one or more cytokines selected from interferon alpha and interleukin-2" and that "a combination of said antisense oligonucleotide and said one or more cytokines is more effective in treating cancer than either component of the combination when used alone." Claims 19, 20, 22, 27-31 and 34 have been cancelled without prejudice or disclaimer, thus rendering moot the Examiner's rejection as it applies to these claims.

Insofar as Examiner's rejection is maintained against amended independent claim 18 and claims dependent thereon, Applicants respectfully traverse for the following reasons. As acknowledged by the Examiner, none of Seheult, Auer, or Abaza teaches or

suggests using an antisense oligonucleotide targeted to ribonucleotide reductase R2. Moreover, Applicants note that none of Seheult, Auer, or Abaza teaches or suggests using the immunotherapeutic agents interferon alpha or interleukin 2. Applicants assert that each of Seheult, Auer, and Abaza in fact teaches a very specific combination therapy intended to achieve a specific end result and that, as such, the skilled worker would not have been motivated to simply substitute one or both agents in the combination, as suggested by the Examiner, with other agents directed to alternate targets or intended to achieve different end effects.

Auer, for example, specifically investigated the response of primary CLL cells to downregulation of the Bcl-2 protein by Bcl-2 phosphorothioate antisense oligonucleotide G3139 in combination with either an antibody (rituximab), or a chemotherapeutic agent (dexamethasone or fludarabine). Nothing in Auer, alone or in combination with Wright-C, teaches or suggests combining an antisense oligonucleotide with a cytokine, much less a combination of an antisense oligonucleotide of at least 7 consecutive nucleotides of the sequence as set forth in SEQ ID NO:1 with interferon alpha or interleukin-2, as recited in amended claim 18.

Seheult teaches a targeted strategy to treating cancer that involves co-expression of IL-12 and an antisense oligonucleotide against TGF-beta1. This approach is based on the premise that concomitant reduction of one cytokine having immunosuppressive properties (TGF-beta1) and augmentation of a second cytokine having immunostimulatory properties (IL-12) would synergistically enhance the immune system and thereby abolish tumor development. Given the very targeted nature of this approach, Applicants assert that Seheult actually teaches away from using an antisense oligonucleotide targeted to any other gene apart from an immunosuppressive cytokine. As such, Applicants assert that Seheult alone or in combination with Wright-C fails to teach or suggest a method of treating cancer with a combination of an antisense

oligonucleotide targeted to ribonucleotide reductase R2 with the cytokines interferon alpha and/or interleukin-2, as recited in independent claim 18.

Abaza investigated whether the inhibition of the proto-oncogene C-myb affected the antineoplastic activity of chemotherapeutic agents (taxol, 5FU, vinblastine and doxorubicin) or immunotherapeutic agents (interferons gamma and beta) towards human colorectal cancer cell lines *in vitro*. As described in Abaza, the C-myb gene was selected as a target for the antisense oligonucleotide as this gene is believed to play a specific role in malignant transformation of colonic mucosa. Abaza describes that a combination of C-myb antisense oligodeoxynucleotides (ODNs) and chemotherapeutic agents (taxol, 5FU, vinblastine and doxorubicin), or immunotherapeutic agents (interferons gamma and beta), resulted in greater inhibition of cell proliferation in colorectal cancer cells than when the two agents were used separately. As such, the authors suggested that C-myb antisense ODNs in combination with antineoplastic drugs may be useful in colorectal cancer therapy.

The teaching in Abaza thus is focussed on a specific target, C-myb, that is useful in the treatment of a specific cancer, colorectal cancer. Applicants assert that given this specific focus of the teaching in Abaza and the specific combinations used, it would not have been obvious to one of ordinary skill in the art at the time the invention was made to replace the antisense oligonucleotide targeted to the C-myb gene with an antisense oligonucleotide (AS-II-626-20 of Wright-B) specifically targeted to a different gene, and furthermore to replace the immunotherapeutic agents interferon gamma and interferon beta of Abaza with interferon alpha or interleukin-2 as recited in amended independent claim 18, nor would the skilled worker, in view of these references, have a reasonable expectation that a combination of this antisense oligonucleotide (targeted to a different gene) with a different immunological agent (*i.e.* interferon alpha and/or interleukin-2) would be more effective in treating cancer than either component of the combination when used alone.

For the reasons outlined above, the Applicants assert that a person skilled in the art, provided with the teachings of Seheult, Auer, and Abaza, in view of Wright-C, would not consider obvious a method of treating cancer using the specifically defined antisense oligonucleotide, i.e., an "antisense oligonucleotide of at least 7 consecutive nucleotides of the sequence as set forth in SEQ ID NO:1" targeted to ribonucleotide reductase R2, specifically in combination with "one or more cytokines selected from interferon alpha and interleukin-2," as recited in amended independent claim 18, nor would the skilled worker, in view of these references, have a reasonable expectation that a combination of this antisense oligonucleotide and the one or more cytokines would be more effective in treating cancer than either component of the combination when used alone. Accordingly, Applicants assert that the combination of Seheult, Auer, or Abaza in view of Wright-C fails to render the subject matter of amended independent claim 18 and claims dependent thereon obvious and that these claims, therefore, comply with 35 USC §103(a).

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested.

Submitted herewith is a Request for Continued Examination and a Petition to extend the period for replying to the Office action for two months, to and including April 5, 2010. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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